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**Deletion of the Imprinted Gene Grb10 Promotes Hematopoietic Stem Cell Self-Renewal and Regeneration.**

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**Public Summary:**

Imprinted genes are unique genes whose functions are dependent on expression from either the maternal or paternal lineage. Importantly, imprinted genes are differentially expressed by adult stem cells, but their functions in regulating adult stem cell fate are incompletely understood. Here we show that growth factor receptor-bound protein 10 (Grb10), an imprinted gene, regulates blood stem cell self-renewal and regeneration. Deletion of the maternal copy of Grb10 in mice substantially increased blood stem cell self-renewal as compared to that of mice expressing both copies of Grb10. After total body irradiation (TBI), mice bearing deletion of the maternal copy of Grb10 demonstrated accelerated stem cell regeneration and blood system reconstitution, as compared to mice expressing both copies of Grb10. Blood stem cells lacking the maternal copy of Grb10 displayed increased proliferation after transplantation or irradiation, commensurate with upregulation of genes that promote cell proliferation, including CDK4 and Cyclin E. Furthermore, the enhanced regeneration of blood stem cells observed in mice lacking a maternal copy of Grb10 was dependent on activation of the Akt/mTORC1 pathway. This study reveals an important function for the imprinted gene Grb10 in regulating blood stem cell self-renewal and regeneration and suggests that the therapeutic inhibition of Grb10 can promote blood stem cell regeneration and blood system recovery after chemotherapy or radiation therapy.

**Scientific Abstract:**

Imprinted genes are differentially expressed by adult stem cells, but their functions in regulating adult stem cell fate are incompletely understood. Here we show that growth factor receptor-bound protein 10 (Grb10), an imprinted gene, regulates hematopoietic stem cell (HSC) self-renewal and regeneration. Deletion of the maternal allele of Grb10 in mice (Grb10m/+ mice) substantially increased HSC long-term repopulating capacity, as compared to that of Grb10+/+ mice. After total body irradiation (TBI), Grb10m/+ mice demonstrated accelerated HSC regeneration and hematopoietic reconstitution, as compared to Grb10+/+ mice. Grb10-deficient HSCs displayed increased proliferation after competitive transplantation or TBI, commensurate with upregulation of CDK4 and Cyclin E. Furthermore, the enhanced HSC regeneration observed in Grb10-deficient mice was dependent on activation of the Akt/mTORC1 pathway. This study reveals a function for the imprinted gene Grb10 in regulating HSC self-renewal and regeneration and suggests that the inhibition of Grb10 can promote hematopoietic regeneration in vivo.

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